Evaluating the use of pathology in improving diagnosis in rural Malawi

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Abstract
Limited data exists on histologically confirmed cancers and tuberculosis in rural Malawi, despite the high burden of both conditions. One of the main reasons for the limited data is the lack of access to pathology services for diagnosis. We reviewed histopathology results of patients in Neno District, one of the poorest rural districts in Malawi, from May 2011 to July 2017, with an emphasis on malignancies and tuberculosis.

Methods
This is a retrospective descriptive study reviewing pathology results of samples collected at Neno health facilities and processed at Kamiza Pathology Laboratory. Data was entered into Microsoft Excel and cleaned and analysed using Stata 14.

Results
A total of 532 specimens were collected, of which 87% (465) were tissue biopsies (incision or core biopsies), and 13% (67) were cytology samples. Of the 532 samples, 72% (n=384) were non-diagnostic results. Among the results that were diagnostic (n=492), 37% (183) were malignancies, 39% (122) were inflammatory conditions other than tuberculosis, 20% (97) were benign tumours, 7% (34) were tuberculosis, 21% (23) were pre-malignant lesions, 5% (23) were normal samples, and 4% (22) were other miscellaneous conditions. Among the malignancies (n=183), 62% (114) were from females and 38% (69) from males. Among females, adenocarcinomas (n=49), followed by Kaposi sarcoma (14%, n=16), skin cancers (9%, n=10), and breast cancer (8%, n=9). In males, Kaposi sarcoma was the most common cancer (35%, n=24), followed by skin cancers (17%, n=12). About 75% (n=137) of the cancers occurred in aged 15 to 60 years.

Conclusion
Histopathology services at a rural hospital in Malawi provides useful diagnostic information on malignancies, tuberculosis and other diagnoses, and can inform management at the district level.

Key words: malignancies, Tuberculosis, Malawi, Neno, pathology

Introduction
Pathological confirmation of some of the major chronic communicable and chronic non-communicable diseases (NCDs) is essential in low and middle-income countries to facilitate early diagnosis and treatment of these conditions1,2. The accessibility and availability of pathology in Malawi should be prioritised, particularly as Malawi begins to face a double burden of chronic communicable and chronic NCDs, which has accelerated the burden of some cancers and communicable and chronic NCDs. It is considered the second most common cause of death, after communicable diseases and injuries (NCDIs), was launched in Malawi in 2006, and has prioritised 37 NCDs to address for its rapid expansion in Africa. This burden on TB and/or malignancies in this rural district. Therefore, we describe here the results obtained from pathology examination of specimens obtained in Neno District, Malawi, from May 2011 to July 2017, with an emphasis on malignancies and TB. Specifically, we aim to contribute to the knowledge gap regarding the significant burden of malignancies and extra-pulmonary TB in Malawi. We present data from a rural setting, which may be one of the first districts in Malawi to have extensive pathology results. We explore the sample turnaround time, diagnostic yield, sample types, and results obtained from all the pathologies during this period.

Methods
Setting
This is a retrospective, descriptive study conducted in the rural district of Neno, in the southwest zone of Malawi. With an estimated population of 165,000 in 20173, Neno has two hospitals and 12 primary health facilities. Most of the 37 NCDs that this study was collected at two hospitals, given that the hospitals had qualified staff, materials, and resources to routinely collect and send samples for pathological examination. The two hospitals are public and therefore free for all at the point of care.

Sample collection
Since 2011, the district has routinely collected and sent samples to Kamiza Pathology Laboratory for pathological examination. Kamiza Pathology Laboratory is a Blantyre-based private laboratory located at least two hours—just over 100 kilometres—away from Neno District. The type and sources of samples were recorded on a standardized laboratory form at the hospital level. Upon collection of the sample, whether sent to Kamiza Pathology Laboratory depending on the next available transport. Currently, single specimens cost 17,820 Malawian Kwacha (MWK) (equivalent to 24 USD in October 2017) and 11,000 MWK (equivalent to 15 USD in October 2017) for histology and cytology examination, respectively.

At the laboratory, samples were accessioned with a unique history or cytology number. The histology samples were processed, paraffin embedded, and Haematoxylin and Eosin (H&E) stained. The cytology samples were air dried or fixed and stained with Pap or Diff Quick stain, as appropriate. The slides were read, and reports generated.

After pathological processing of the samples and interpretation of the slides, all results were sent to Neno as soft copies through email to facilitate quick decision making. Hard copies were then collected by the Neno staff weekly.

Data management, outcomes, and analysis
All results from May 2011 to July 2017 were retrieved from pathology laboratory forms, and entered into a Microsoft Excel database. We present age and gender demographics of the patients, sample turnaround time, site and specimen types, and final diagnosis of the pathology examination. As there can be variations in the definition of turnaround time, we defined turnaround time as the time the sample was collected to the time the result was reported back to the laboratory. This turnaround time combined times from sample collection by the health workers, temporary storage at Neno laboratory, transportation to Kamiza pathology, laboratory sample collection and processing, and the time to results being reported by the laboratory. We categorized sample types as either histology or cytology. Histology samples included open and core needle biopsies. Cytology samples included fine needle aspiration biopsies, liquid-based examination of the specimen.

All results were classified as either diagnostic or non-diagnostic. Non-diagnostic results were where the samples were not representative, were inadequate, or were not useful to make the diagnosis and required repetition of the examination. All malignancies were defined as diagnostic results and were further sub-classified as malignant, premalignant, benign lesion, tuberculosis, extra-pulmonary TB and other infectious conditions, and normal results. With specific emphasis on malignant and tuberculosis samples, we describe sample site and type, gender, and age category (0-14 years, 15-60 years, and over 60 years) of the cases.

All data were entered into Microsoft Excel. Data cleaning and analysis occurred in Stata 14 by StatCorp LP. We used descriptive statistics to describe our outcomes.

Ethical considerations
The study was covered by the National Health Sciences Research Committee #1216 and the local Ministry of Health.

Results
Between May 2011 and July 2017, 532 specimen results were reviewed. The average turnaround time for results was 3.7 days (N= 531, range: 0.35 days). Of all specimens, 87% (n=465) were histology samples and 13% (n=67) were cytology samples.

About 92% (n=492) of all samples were diagnostic. Among diagnostic results, 37% (n=183) were malignant, 23% (n=112) were infections and inflammatory conditions, 20% (n=107) were other miscellaneous conditions, 4% (n=22) were due to other miscellaneous conditions, and 4% (n=21) were premalignant lesions (Figure 1). Only 3% (n=5) were normal. Among the non-diagnostic samples, 65% (n=26) were histology and 35% (n=14) were cytology.

Of the diagnostic results that were identified as malignant (n=21), 76% (n=16) were lesions from the cervix, followed by atypical endometrial dysplasia (14%, n=3) and dysplasia of skin (10%, n=2).

The most common sample collection sites for malignancies were skin (30%, n=55), cervix (27%, n=50), lymph nodes (16%, n=30), breast (5%, n=9), and penis (5%, n=6). Among malignancies, 56% (n=101) were skin cancers, 51% (n=97) were breast cancers, 49% (n=94) were cervical cancers, 27% (n=51) were Kaposi sarcoma (22%, n=40), cancers of the skin (12%, n=22), Hodgkin’s lymphoma (5%, n=10), secondary lymph node cancers (5%, n=10), non-Hodgkin’s lymphomas (5%, n=9), and squamous cell carcinoma of skin (5%, n=9) were the most common cancers (Table 1). By age category, 75% of all cancers occurred in patients between the ages of 15-60 years. Females accounted for 65% (n=114) of all cancer patients.
Cervical cancer was the most common cancer in females, contributing to nearly half of all cancers (43%, n=49). The next most prevalent types of cancers in females were Kaposis sarcoma (14%, n=16) and skin cancer (9%, n=10). Breast cancer in females was more common than lymphomas, secondary lymph node cancers, and other cancers combined for all the types of cancer in females. In contrast, Kaposis sarcoma was the most common cancer in males, contributing to over one third of all cancers (35%, n=24), followed by skin cancer (17%, n=12) and Hodgkin’s lymphoma (12%, n=8). The rest of the cancers contributed to 10% or less of the total cancers males. Only two cases—both females—were found to have oesophageal cancer.

Based on histological subtypes, there was diversity around the types of cervical, skin, and secondary lymph node cancers. For cervical cancers (n=49), 84% (n=41) were squamous cell carcinoma, 14% (n=7) were adenocarcinoma, and 2% (n=1) were not specified. For skin cancers (n=22), 64% (n=11) were malignant melanomas, followed by squamous cell carcinoma (32%, n=7) and basal cell carcinoma (9%, n=2)—the rest were other types of cancers. Squamous cell carcinoma was the most common type of secondary lymph node cancer, contributing to half of all cancers (50%, n=5) and adenocarcinoma (n=2) and other non-specified carcinomas (n=3) representing the rest of the samples.

A TB diagnosis was made in 34 samples, or 7% of the total samples. The most common site for TB was the abdomen, contributing to 81% (n=27) of the samples, followed by skin, and secondary lymph node cancer, contributing to half of all lymph node cancers. The most common type of cancer in the samples that were sent for pathological analysis was tuberculosis (7%, n=2), followed by squamous cell carcinoma (5%, n=1). The high degree of these diagnoses suggest little waste in the pathology support as it is set up in Neno District.

Although it was not possible to investigate pre-biopsy diagnosis of patients in this study, we know from one study in Blantyre that cancer can be clinically misdiagnosed as TB due to inadequacy of pathology services in pre-referral and primary care settings15, which was diagnosed mainly on clinical suspicion, resulted in wrong diagnoses and delays in cancer diagnoses by up to 5 months. If pathology services were not available in Neno, it is probable that one of the cancer patients included in this study would have been similarly misdiagnosed and experienced delayed diagnoses. Similarly, we do not have pre-biopsy diagnoses for the patients diagnosed with TB in this study, so we cannot ascertain the likelihood of whether these patients would have been treated presumptively for TB or if they would have remained undiagnosed. However, TB case notification rates in both Neno and Malawi generally are lower than expected, and we posit that biopsy as an additional case-finding mechanism could contribute to an increase in case notification rates16.

Based on the high yield of results in this study, we recommend that clinically suspected lesions in a rural district should be biopsied and sent for pathological examination, to ensure an accurate diagnosis and hopefully impact treatment decisions. As much as possible, we would encourage abandoning clinical suspicion for cancers in favour of pathological confirmation to allow for accurate cancer and TB diagnosis. It is therefore essential that district hospitals in Malawi have access to high-quality and timely pathological services to achieve this goal. The turnaround time in Neno is much lower than that reported in other studies in urban areas, where average times have been reported to be as high as 18 days for paid samples and 43 days for non-paid samples in one study in Blantyre17. As Neno District has no dedicated transport for pathology samples to Blantyre, the district relies on transport support from both the Ministry of Health and PHIL, who routinely transport samples with any vehicle that is going to Blantyre. Additionally, the results from the laboratory are immediately emailed to the Neno laboratory and clinical teams. This allows the team to have the results as soon as they are reported.

In this review, cervical cancer and Kaposis sarcoma were the two main cancers in both sexes, with cervical cancer being more common in females and Kaposis Sarcoma being more common in males. This is similar to a population-based cancer prevalence study in Malawi, as well as other comparable studies, although our sample is likely biased towards women attending hospital in a district hospital setting18-19. However, in these studies, oesophageal cancer it often reported as the third most common cancer18,19. In fact, one study at a referral hospital estimated that oesophageal cancer is the most common cancer20. However, in our study, only two cases of oesophageal cancer were found within the time period studied. This discrepancy between pathology results for the diagnosis of cancers and TB in a rural district of Malawi. This data adds to the body of literature about TB, premalignant conditions, and cancers in Malawi, particularly amongst a rural and impoverished population.

In this study, cancers alone contributed to 4 out of 10 samples that were sent for pathological analysis. By adding premalignant conditions to the nearly half of all biopsies in Neno were diagnostic for these conditions. The high degree of these diagnoses suggest little waste in the pathology support as it is set up in Neno District.

Although we explored some demographic characteristics of TB and malignancy patients in our sample, we did not ascertain the HIV status of the cases. There is evidence from literature about TB, premalignant conditions, and cancers, and other cancers combined for all types of cancers in females. In contrast, Kaposis sarcoma was the most common cancer in males, contributing to over one third of all cancers (35%, n=24), followed by skin cancer (17%, n=12) and Hodgkin’s lymphoma (12%, n=8). The rest of the cancers contributed to 10% or less of the total cancers males. Only two cases—both females—were found to have oesophageal cancer.

Table 1: Common malignancies in Neno

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>N (%)</th>
<th>Female (N, %)</th>
<th>Male (N, %)</th>
<th>Below 15 (N, %)</th>
<th>15-60 (N, %)</th>
<th>Over 60 (N, %)</th>
<th>N, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>49 (26.8)</td>
<td>49 (43.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>35 (25.5)</td>
<td>13 (40.6)</td>
<td>10 (66.7)</td>
</tr>
<tr>
<td>Kaposis sarcoma</td>
<td>40 (21.5)</td>
<td>16 (40)</td>
<td>24 (60)</td>
<td>3 (30)</td>
<td>35 (25.5)</td>
<td>1 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Skin cancer</td>
<td>22 (12.0)</td>
<td>10 (45.5)</td>
<td>12 (45.5)</td>
<td>1 (4.5)</td>
<td>15 (68.1)</td>
<td>6 (27.3)</td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>10 (5.5)</td>
<td>6 (58.1)</td>
<td>4 (36.4)</td>
<td>1 (10)</td>
<td>4 (39.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>9 (4.9)</td>
<td>3 (33.3)</td>
<td>6 (66.7)</td>
<td>0 (0)</td>
<td>9 (88.8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>9 (4.9)</td>
<td>9 (90)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>8 (88.8)</td>
<td>1 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Perine</td>
<td>6 (3.3)</td>
<td>6 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6 (100)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>5 (2.6)</td>
<td>5 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (100)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>4 (2.2)</td>
<td>3 (75)</td>
<td>1 (25)</td>
<td>1 (25)</td>
<td>2 (50)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal cancer</td>
<td>4 (2.2)</td>
<td>4 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (100)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>10 (5.5)</td>
<td>6 (60)</td>
<td>4 (40)</td>
<td>0 (0)</td>
<td>7 (70)</td>
<td>3 (30)</td>
<td></td>
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</table>

Table 2: Tuberculosis cases in Neno

<table>
<thead>
<tr>
<th>Type of TB</th>
<th>Total</th>
<th>N, %</th>
<th>Female (N, %)</th>
<th>Male (N, %)</th>
<th>N, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node</td>
<td>19 (55.9)</td>
<td>16 (68)</td>
<td>3 (12)</td>
<td>4 (44.4)</td>
<td>14 (69.9)</td>
</tr>
<tr>
<td>Skin and soft tissue</td>
<td>7 (20.6)</td>
<td>5 (71)</td>
<td>2 (28)</td>
<td>3 (33.3)</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>3 (8.8)</td>
<td>1 (33)</td>
<td>2 (67)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Chest</td>
<td>3 (8.8)</td>
<td>2 (67)</td>
<td>1 (33)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Breast</td>
<td>2 (5.5)</td>
<td>1 (50)</td>
<td>1 (50)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>34 (100)</td>
<td>19 (56)</td>
<td>15 (44)</td>
<td>9 (26)</td>
<td>23 (68)</td>
</tr>
</tbody>
</table>

Figure 1: Pathology diagnostic results in Neno

Conclusions

The results presented here describe the burden and distribution of histologically confirmed cancer and tuberculosis at district level health facilities in rural Malawi. Since TB, premalignant lesions, and cancers, contribute to nearly half of all pathology samples from a rural hospital, we advocate for routine use of pathology at all district hospitals.

Conflict of interest

Dr Steve Kamiza is the owner of Kamiza Pathology Laboratory. The services in Neno was set up in 2011 as part of routine clinical services and the pathology laboratory. The pathology laboratory was chosen based on closest available pathology laboratory during that time. The decision to inform all authors, including Dr Steve Kamiza, of this manuscript’s design and preparation was made after he was hired as a hospital in a district hospital setting. However, in these studies, oesophageal cancer it often reported as the third most common cancer. In fact, one study at a referral hospital estimated that oesophageal cancer is the most common cancer. However, in our study, only two cases of oesophageal cancer were found within the time period studied. This discrepancy between Neno and data from across the rest of the country may be due to an inability in our facilities to obtain oesophageal samples, since this technique is not performed at many public district hospitals. This is therefore an important area of future study and intervention.

With the difficulties in diagnosing TB—particularly extra-pulmonary TB—biopsies provide an alternative method, especially for at-risk populations such as lymph nodes. As evidenced in this study, 7% of our cases had a diagnosis of TB. Additionally, biopsies may help to reduce the misdiagnosis of TB when patients actually have malignancies, a scenario reported in Blantyre.

Although we explored some demographic characteristics of TB and malignancy patients in our sample, we did not ascertain the HIV status of the cases. There is evidence from literature about TB, premalignant conditions, and cancers, and other cancers combined for all types of cancers in females. In contrast, Kaposis sarcoma was the most common cancer in males, contributing to over one third of all cancers (35%, n=24), followed by skin cancer (17%, n=12) and Hodgkin’s lymphoma (12%, n=8). The rest of the cancers contributed to 10% or less of the total cancers males.
declare.

Author contributions
CK conceptualized the study and performed data cleaning and analysis. AP and FM collected and entered the data. CK wrote the first draft. All authors contributed to the study and approved the final version for publication.

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